Urinary neutrophil gelatinase-associated lipocalin-guided risk assessment for major adverse kidney events after open-heart surgery

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Aim: To assess whether doctors' clinical risk-assessment for major adverse kidney events (MAKE) and acute kidney injury (AKI) after open-heart surgery would improve when being informed about neutrophil gelatinase-associated lipocalin (NGAL) test result at ICU admission. **Patients & Methods:** Clinical risk-assessment for MAKE and AKI were performed with and without providing NGAL test result and compared in an exploratory- and a validation-cohort using reclassification metrics, exemplary category-free net reclassification improvement (cfNRI). **Results:** Exploratory cohort: doctors' prediction of MAKE (cfNRI = 0.750 [0.130–1.370]; $p = 0.018$) and AKI (cfNRI = 0.565 [0.001–1.129]; $p = 0.049$) improved being provided with NGAL test information. This finding was confirmed in the validation-cohort (MAKE cfNRI = 0.930 [0.188–1.672]; $p = 0.014$) and the combined-cohort (MAKE: cfNRI = 0.847 [0.371–1.323], $p < 0.001$; AKI: cfNRI = 0.468 [0.099–0.836]; $p = 0.013$). Improvements mostly generated from correctly reclassifying patients who not developed events ($p < 0.001$). **Conclusion:** Biomarker informed risk-assessment is superior in predicting MAKE and AKI after open-heart surgery.

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Acute kidney injury (AKI) is a common and serious complication in patients undergoing cardiac surgery with incrementally worsening prognosis [1].

Early assessment of risk for major adverse kidney events (MAKE) and AKI by the treating physician is a part of routine care in open-heart surgery patients. Accordingly, the most recent AKI clinical practice guidelines emphasize the importance of achieving the earliest possible identification of such risk [2]. Clinical assessment of AKI risk is based on acute and chronic health condition and routinely obtained clinical (e.g., hemodynamic status and urinary output) and biochemical parameters (e.g., serum creatinine). Recently, novel kidney injury biomarkers have been included in AKI risk assessment to complement an established renal functional criteria [3]. However, if and to what extent, knowledge of novel urinary biomarkers can improve risk assessment for MAKE after cardiac surgery is important but unknown.

Figure 1. Patient flow diagram. In the exploration cohort, renal risk assessment was done retrospectively, in detail with the risk assessor being provided with key variables (Table 1). In the validation cohort, renal risk assessment was done prospectively at the bedside with the risk assessor being provided with available clinical variables (Table 1).

Among early kidney tubular damage or stress biomarkers [4], the most comprehensive data on diagnostic and prognostic performance is available for urinary neutrophil gelatinase-associated lipocalin (NGAL) [5,6]. NGAL is readily available on clinical laboratory platforms and among other settings [7] appears of considerable discriminatory value for prediction of adverse kidney-related events after an open-heart surgery [8–10].

We hypothesized, that after open-heart surgery, doctors' risk assessment for MAKE and AKI would improve when being informed about NGAL test result (risk assessment with biomarker & clinical information, B&CI) versus conventional clinical risk assessment (CCA) without information about NGAL test result.

Patients & methods

Reporting this study, the 'Strengthening the Reporting of Observational Studies in Epidemiology' recommendations were followed [11].

Patient population

The study consisted of an exploratory cohort and a validation cohort (Flowchart, Figure 1). Both cohorts enrolled patients who underwent nonemergency open-heart surgery with cardiopulmonary bypass.

The purpose of the exploratory cohort was to retrospectively validate the concept of kidney-centered clinical risk assessment in cardiac surgery patients. In this cohort, using patient medical records, we asked the risk assessor to adjudicate relevant outcomes first using CCA and thereafter, using combined biomarker NGAL test result with clinical information (B&CI). The purpose of the validation cohort was to prospectively compare these two approaches of risk assessment (NGAL-informed [B&CI] vs NGAL-uninformed [CCA]) at the bedside.

Exploratory cohort

The exploratory cohort of this study used the control group ($n = 100$ patients, Figure 1) of a previous randomized study, the 'BIC-Multicenter Study' at the 'German Heart Center, Berlin' (NCT00672334). In brief, the previous study explored in a multicenter, double-blinded, randomized controlled design whether prophylactic sodium bicarbonate infusion (intervention group) would reduce the incidence of AKI and tubular damage compared with sodium chloride infusion (control group) in patients undergoing open-heart surgery. Full study details were described previously [12]. Local institutional Review Board (Medicine Ethics Committee, Charité University, Berlin, Germany: ZS EK 11 654/07) and written informed consent was obtained from each patient.

Validation cohort

We enrolled a prospective clinical validation cohort (Figure 1), which included 101 consecutive adult patients undergoing an open-heart surgery at the University-Clinic Magdeburg, Germany. The local institutional Review Board categorized this study as an audit of current clinical practice and approved prospective data collection and use for the purpose of the study (Ethics Committee, University of Magdeburg, Case 49/13).

Exclusion criteria

In both patient cohorts, we excluded patients undergoing emergency operation (time between hospital admission to operation <24 h) or off-pump surgery, those presenting with advanced chronic kidney disease (serum creatinine >300 $\mu\text{mol/l}$) or kidney transplant and patients <18 years, patients on immunosuppression and those enrolled in conflicting research study. In both cohorts, decisions for all diagnostic and therapeutic interventions were made by the intensive-care physicians, independent of this investigation.

Major adverse kidney events

The primary study end point was the prediction of MAKE occurring until hospital discharge. MAKE included 'renal risk, injury, failure, loss of renal function, end stage renal disease classification'-based (RIFLE) [13] stages 'Injury' or 'Failure', persistent AKI (>48 h), acute renal replacement therapy (RRT) initiation and in-hospital mortality.

The secondary end point was the prediction of AKI, defined and classified by severity according to the RIFLE stages 'Risk', 'Injury' or 'Failure'. RIFLE criteria were based on increases of postoperative serum creatinine from preoperative baseline value as well as urinary output criteria [13]. We chose RIFLE criteria because literature indicates a trend for higher discriminative value in predicting hospital mortality in cardiac surgery patients compared with AKIN (Acute Kidney Injury Network) or KDIGO (Kidney Disease Improving Global Outcome) criteria [14,15]. Primary and secondary end points were adjudicated by two independent expert nephrologists who were blinded to the clinical risk assessor's adjudication and NGAL test results. Disagreements were resolved by a third opinion.

Acute RRT was initiated following criteria applied in the 'RENAL' study [16] if the patient fulfilled at least one of the following clinical criteria: oliguria (urinary output <100 ml/6 h) that was unresponsive to fluid resuscitation measures, hyperkalemia ($[\text{K}^+] >6.5$ mmol/l), severe acidemia ($\text{pH} <7.2$) or clinically significant organ edema (e.g., lung) in the setting of renal failure.

Procedures for clinical risk assessment

In both, the exploratory cohort (retrospective, outcome-blinded adjudication using medical records including information until ICU admission) and the validation cohort (prospectively performed end point prediction at the bedside at the time of ICU admission), the same outcome-blinded renal risk assessor (consulting nephrology physician) estimated the risk (in percent) of potential adverse events (MAKE, AKI) occurring during the index admission.

Renal risk assessment was done by the risk assessor on the basis of all complete perioperative clinical information available until 1 h after ICU admission (conventional clinical risk assessment without information on NGAL-test result, CCA), for example, hemodynamic status (i.e., continuous cardiac index, mean arterial pressure- and central venous pressure-monitoring), urinary output and biochemical parameters in patient records (exploration cohort) or at the bedside (validation cohort) (Table 1), respectively and was repeated by the same risk assessor after being informed of the NGAL test result measured at ICU admission (B&CI).

Specifically, in the exploratory cohort, the risk assessor was provided with all necessary clinical details obtained from the patient record until 1 h after ICU admission, but he was blinded for any events thereafter. In the validation

Table 1. Perioperative patients' characteristics in both study-cohorts.

Variable	Exploratory cohort				Validation cohort			
	No RIFLE-AKI (n = 91)	RIFLE-AKI (n = 9)	MAKE (n = 9)	P [†] AKI vs No AKI	No RIFLE-AKI (n = 88)	RIFLE-AKI (n = 13)	MAKE (n = 7)	P [†] AKI vs No AKI
Age, years	67 (56–73)	74 (70–74)	74 (70–77)	0.015	71 (62–76)	70 (61–77)	62 (60–73)	0.996
Sex, female, n (%)	31 (34.1)	2 (22.2)	3 (33.3)	0.377	24 (27.3)	4 (30.8)	5 (71.4)	0.751
Diabetes mellitus on medication, n (%)	34 (38.6)	8 (61.5)	4 (57.1)	0.004	17 (18.7)	3 (33.3)	3 (33.3)	0.717
Arterial hypertension, n (%)	65 (71.4)	8 (88.9)	7 (77.8)	0.439	87 (97.8)	12 (92.3)	6 (85.7)	0.339
Preoperative serum creatinine, $\mu\text{mol/l}$	87 (78–105)	88.0 (77.0–127.5)	105 (77–159)	0.558	83.0 (72.0–101.5)	133 (93–175)	127 (75–175)	0.001
Preoperative eGFR ml/min/1.73/m ² , CKD-EPI	71.9 (57.2–86.9)	57.1 (48.3–85.1)	53.6 (38.5–85.1)	0.226	75.9 (61.0–89.8)	42.6 (32.0–70.1)	48 (33.5–74.9)	<0.001
Left ventricular dysfunction, n (%) [‡]	15 (16.5)	4 (44.4)	4 (44.4)	0.064	42 (47.7)	10 (76.9)	5 (71.4)	0.073
Procedures				0.949				0.151
CABG surgery, n (%)	17 (18.7)	2 (22.2)	2 (22.2)		42 (47.7)	6 (46.2)	2 (28.6)	
Valvular surgery, n (%)	45 (49.5)	4 (44.4)	3 (33.3)		28 (31.5)	2 (15.4)	1 (14.3)	
CABG and valvular surgery, n (%)	22 (24.2)	3 (33.3)	4 (44.4)		16 (18.2)	4 (30.8)	3 (42.9)	
Thoracic aortic surgery, n (%)	7 (7.7)	0 (0)	0 (0)		0 (0)	1 (7.7)	1 (14.3)	
Valvular and aortic surgery, n (%)	0 (0)	0 (0)	0 (0)		3 (3.4)	0 (0)	0 (0)	
Redo cardiac surgery, n (%)	26 (28.6)	2 (22.2)	1 (11.1)	0.514	3 (3.4)	0 (0)	0 (0)	1.000
Duration of cardiopulmonary bypass, min	119 (93–144)	147 (112–247.5)	147 (129–248)	0.036	86 (61.3–108.8)	99 (77.5–129)	104 (91–148)	0.087
Adverse outcome								
Postoperative renal replacement therapy, n (%)	2 (2.2)	3 (33.3)	5 (55.6)	0.005	0 (0)	6 (46.2)	6 (85.7)	<0.001
In-hospital mortality, n (%)	0 (0)	3 (33.3)	3 (33.3)	0.001	0 (0)	3 (23.1)	3 (42.9)	0.002
MAKE, n (%)	2 (2.2)	7 (77.8)	–	<0.001	0 (0)	7 (53.8)	–	<0.001

Numbers denote median (25.–75. percentile) or frequency (%) where appropriate.

[†]p-value refers to comparison of patients with no AKI versus those with AKI.

[‡]Left ventricular ejection fraction <35%.

AKI: Acute kidney injury; CABG: Coronary artery bypass graft; CKD-EPI: Chronic kidney disease epidemiology collaboration; eGFR: Estimated glomerular filtration rate; MAKE: Major adverse kidney event; RIFLE: Risk injury failure end-stage renal disease classification.

cohort, the risk assessor performed risk assessment (without NGAL) and reassessment (with NGAL) at the bedside 1 h after ICU admission and was provided with all necessary clinical details so far. So, he was blinded for any events thereafter.

By the risk assessor kidney biomarker test results were included in clinical risk assessment on the understanding that higher kidney biomarker concentrations likely reflect more severe kidney injury [17].

Biomarker sampling: exploratory cohort

Sampling was performed in detail as previously described [12]. We obtained urine at baseline and at 6 h (referred to as 'ICU admission' value) after commencement of cardiopulmonary bypass. Urine was frozen at -80° and measured in a badge analysis.

Biomarker sampling: validation cohort

Urinary NGAL was sampled at ICU admission in each patient and measured within 60 min as described below.

Biomarker measurement

In both the cohorts, biomarker measurements were performed on standardized clinical platform for urinary NGAL (ng/ml, ARCHITECT®, Abbott Diagnostics, IL, USA), a CE-certified biomarker for supplementing AKI diagnosis in Germany. CE certification mark indicates conformity with health, safety and environmental protection standards for products sold within the EEA. In the validation cohort NGAL test results were available within one hour after sampling in central pathology. Laboratory investigators of both cohorts were blinded to the sample sources and clinical outcome.

Statistical analysis

For assessment and comparison of doctors' clinical risk assessment (in percent): without and subsequently; with knowledge of NGAL test result were regarded as reference and new risk prediction, respectively. Reference and new risk prediction was assessed using established statistical methods including the area under the receiver operating characteristic curve (AUC-ROC), net reclassification improvement (NRI) and integrated discrimination improvement (IDI) as reported in previous studies [18,19]. The predictive performance of both clinical risk assessments was reported as AUC-ROC with 95% CI. Comparisons of clinical risk assessments were accomplished with SAS for Windows, version 9.4, PROC Logistic. Improvements in the performance of doctors' risk assessment being informed on NGAL test result and clinical information (B&CI) compared with CCA were evaluated by net reclassification improvement (reported as category free, cfNRI [derived from formula 1]) and by IDI [20]. Effect estimates were completed with p-values from asymptotic tests versus zero (no change in quality of prediction) [21]. Mann–Whitney U-test, Pearson's χ^2 test or Fisher exact test were used for exploratory comparisons between patients. A two-sided p-value of <0.05 was considered to be statistically significant.

For all these additional analyses, we used SPSS for Windows, version 22.0 (IBM Corp., NY, USA).

$$NRI = \frac{\text{events reclassified higher} - \text{events reclassified lower}}{\text{sum of total events}} + \frac{\text{nonevents reclassified lower} - \text{nonevents reclassified higher}}{\text{sum of nonevents}} \quad \text{Formula 1.}$$

Results

Patient characteristics

A summary of baseline characteristics of both patient cohorts is shown in Table 1. Exploratory and validation cohorts were similar regarding sample size, age, type of comorbidities and event rates. Patients in the validation cohort more frequently underwent coronary artery bypass graft with shorter duration 'on-pump' compared with the exploration cohort, likely reflecting center-specific surgical preferences. AKI was associated with increased in-hospital mortality and initiation of renal replacement therapy (RRT) (Table 1).

Risk assessment in patient cohorts using CCA & B&CI

For both cohorts, performance of the reference model (CCA) and change of risk assessment using combined clinical information and urinary NGAL test result (B&CI) for prediction of MAKE and AKI is shown in Table 2 & Figures 2 & 3. Two general trends were observed. First, after addition of NGAL, cfNRI showed significant improvements in correctly reclassifying patients with regard of the clinical end points MAKE and AKI, whereas IDI showed only moderate improvements. Second, cfNRI improvements were largely based on improvements in the correct reclassification of MAKE- and/or AKI-free (event-free) patients after information about NGAL test result was provided to the risk assessor.

Table 2. Category-free net reclassification improvement, integrated discrimination improvement and area under the receiver operating characteristic curve of combined biomarker (neutrophil gelatinase-associated lipocalin) and clinical information compared with conventional clinical assessment.

	Exploration cohort		Validation cohort		Combined cohort	
	B&CI vs CCA	p-value	B&CI vs CCA	p-value	B&CI vs CCA	p-value
MAKE as dependent variable						
cfNRI	0.750 (0.130–1.370)	0.018	0.930 (0.188–1.672)	0.014	0.847 (0.371–1.323)	0.0005
cfNRI _{events}	0.222 (-0.376 to 0.821)	0.467	0.143 (-0.590 to 0.876)	0.703	0.188 (-0.278 to 0.653)	0.430
cfNRI _{nonevents}	0.528 (0.365–0.690)	<0.0001	0.787 (0.674–0.901)	<0.0001	0.660 (0.559–0.760)	<0.0001
IDI	-0.018 (-0.095 to 0.059)	0.655	-0.027 (-0.088 to 0.035)	0.394	-0.022 (-0.072 to 0.269)	0.374
IDI _{events}	0.015 (-0.060 to 0.089)	0.697	0.017 (-0.043 to 0.077)	0.576	0.016 (-0.032 to 0.064)	0.517
IDI _{nonevents}	-0.032 (-0.053 to 0.012)	0.002	-0.044 (-0.055 to 0.033)	<0.0001	-0.038 (-0.050 to 0.027)	<0.0001
AUC _{reference}	0.845 (0.726–0.965)		0.736 (0.491–0.980)		0.798 (0.674–0.923)	
AUC _{new}	0.887 (0.770–1.000)		0.876 (0.768–0.985)		0.872 (0.793–0.950)	
AUC _{difference}	0.042 (-0.073 to 0.156)	0.477	0.141 (-0.04 to 0.324)	0.132	0.073 (-0.017 to 0.163)	0.111
AKI as dependent variable						
cfNRI	0.565 (0.001–1.129)	0.049	0.441 (-0.027 to 0.908)	0.065	0.468 (0.099–0.836)	0.013
cfNRI _{events}	0.444 (-0.099 to 0.988)	0.109	0.077 (-0.373 to 0.527)	0.738	0.227 (-0.128 to 0.582)	0.209
cfNRI _{nonevents}	0.121 (-0.031 to 0.273)	0.119	0.364 (0.237–0.490)	<0.0001	0.240 (0.140–0.341)	<0.0001
IDI	0.0744 (-0.059 to 0.208)	0.274	-0.021 (-0.085 to 0.043)	0.517	0.019 (-0.049 to 0.086)	0.591
IDI _{events}	0.108 (-0.021 to 0.236)	0.099	0.019 (-0.042 to 0.080)	0.536	0.056 (-0.009 to 0.120)	0.092
IDI _{nonevents}	-0.033 (-0.069 to 0.002)	0.065	-0.041 (-0.061 to 0.020)	0.0001	-0.037 (-0.057 to 0.016)	0.0004
AUC _{reference}	0.744 (0.608–0.880)		0.758 (0.618–0.898)		0.749 (0.655–0.844)	
AUC _{new}	0.823 (0.659–0.987)		0.842 (0.735–0.948)		0.825 (0.736–0.915)	
AUC _{difference}	0.079 (-0.065 to 0.222)	0.281	0.084 (-0.019 to 0.187)	0.110	0.076 (0.000–0.151)	0.049

IDI and cfNRI refer to the improved reclassification of patients using the reference (CCA) compared with the new risk prediction (B&CI).
AUC: Area under curve; AKI: Acute kidney injury; B&CI: Biomarker & clinical information combined; CCA: Conventional clinical risk assessment; cfNRI: Category-free net reclassification improvement; IDI: Integrated discrimination improvement; MAKE: Major adverse kidney event.

Specifically, in the exploratory cohort, risk prediction including information about NGAL test result (B&CI) significantly improved prediction compared with CCA for MAKE (cfNRI 0.750 [0.130–1.370]; $p = 0.018$) and AKI (cfNRI 0.565 [0.001–1.129]; $p = 0.049$), respectively (Figure 2). This finding was confirmed in the validation cohort (cfNRI–MAKE 0.930 [0.188–1.672], cfNRI–AKI: 0.441 [0.027–0.908]) (Figure 2 & Table 1). In the combined cohort, B&CI for MAKE showed improvements in the new model with cfNRI of 0.847 (0.371–1.323; $p < 0.001$) and cfNRI of 0.468 (0.099–0.836); $p = 0.013$ for AKI.

In the exploration cohort, however, reclassification effects for AKI were larger with event-patients (0.444 [-0.099–0.988] vs 0.121 [-0.031 to 0.273] for non-event), yet they were not significant because of few events in this cohort.

In the combined cohort B&CI-improved cfNRI for MAKE or AKI predominantly based on correct reclassification of event-free patients (MAKE: 0.660 [0.559–0.760]; $p < 0.001$; AKI: 0.240 [0.140–0.341]; $p < 0.001$), Table 2. IDI values in both the cohorts confirmed significant reclassification of event-free patients (MAKE, AKI) if assessment was based on NGAL test result using B&CI (all p -values < 0.001). In the combined cohort, the AUC for the ROC curve for MAKE nonsignificantly improved from 0.798 to 0.872; $p = 0.111$ and for AKI, AUC-ROC improved from 0.749 to 0.825, $p = 0.049$, cfNRI 46.8 (Table 2 & Figure 3).

Discussion

Key findings

In patients after open-heart surgery, we compared risk assessment for MAKE or AKI with either conventional clinical assessment (CCA) with doctor's assessment being informed about NGAL test result in addition to clinical information (B&CI). Providing the risk assessor with NGAL test result, improved expert physician's clinical

Figure 2. Risk assessment plots showing the additional value of urinary NGAL measured at ICU admission for conventional clinical risk assessment for major adverse kidney events and acute kidney injury before (CCA) (● nonevents [green], ■ events [red]) and after (● nonevents [blue], ■ events [orange]) providing the risk assessor with the neutrophil gelatinase-associated lipocalin test result (B&CI). Squares ■ represent sensitivity versus the calculated risk for those with the event whereas circles ● represent 1-specificity versus the calculated risk for those without an event.

AKI: Acute kidney injury; B&CI: Biomarker & clinical information combined; CCA: Conventional clinical risk assessment; MAKE: Major adverse kidney event; NGAL: Neutrophil gelatinase-associated lipocalin.

risk assessment for MAKE and AKI in the exploratory and the validation cohort. Finally, we found that such reclassification predominantly increased the number of correctly identified patients with no events.

Relationship with previous studies

NGAL measured in urine shows major changes in patients subsequently developing AKI after open-heart surgery and has been previously reported to be of value in the prediction of kidney-related outcomes [8,22]. A previous study assessed the ability of NGAL as prognostic marker without evaluating complex process of clinical risk assessment through a clinician (as was the study question of our study). They found modest clinical utility of NGAL when used as isolated kidney biomarker [23]. Di Somma and colleagues previously reported improved diagnostic performance when NGAL was added to clinical judgement in a multivariate model (AUC improved from 0.837 to 0.900; NRI = 32.4). However NGAL test results [24] or results of other biomarkers, such as cell cycle arrest markers [25] were not incorporated in a physicians' risk assessment at the bedside. We analyzed the potential of NGAL to directly improve clinician's risk assessment in addition to usual relevant clinical/pathology information. Given their

Figure 3. Improvement in clinical risk assessment at ICU admission of the retrospective evaluated exploration cohort and prospective validation cohort. Receiver operator characteristic curves for prediction of clinical end points (major adverse kidney events and acute kidney injury) of urinary NGAL and nephrology consultant as renal risk assessor before (blue curve) and after (purple curve) informing about neutrophil gelatinase-associated lipocalin test results (corresponding area under curve values are shown in Table 2). AKI: Acute kidney injury; AUC: Area under curve; CCA: Conventional clinical risk assessment; MAKE: Major adverse kidney event; NGAL: Neutrophil gelatinase-associated lipocalin; ROC: Receiver operating characteristic curve.

predictive ability for AKI and MAKE being similar to that of NGAL, markers of glomerular function decline, such as Serum Cystatin [26] or other tubular cell stress or damage markers [27,28], such as cell cycle arrest markers [29] may have also worked for improving clinicians' risk assessment. However, this hypothesis using one or more of the above-mentioned biomarkers still needs to be further investigated [30].

Thus, to the best of our knowledge, this is the first study to report on a biomarker test result-informed clinical risk assessment of patients undergoing open-heart surgery.

Implications of study findings

Early recognition of AKI or subclinical AKI [31,32] using NGAL test result at the bedside may help guiding early risk-stratified interventions such as implementation of the KDIGO care bundles [33], but also avoid unnecessary care for event-free patients. In some cases with very high NGAL concentrations in a given clinical context, even earlier institution of renal replacement therapy may be justified [34]. But such approach would need confirmation in future research on biomarker test result-informed clinical decision-making.

Study strengths & limitations

This study has several strengths. All clinical experts performing outcome adjudication for AKI and MAKE as well as the clinical risk assessor and laboratory personnel performing NGAL tests were blinded to patients' outcome. Patient-cohorts were obtained from two separate university medical centers, thus providing a degree of external validity. To assess improvements of renal risk assessment at the bedside, our findings were addressed and verified in a prospective confirmation study utilizing urinary NGAL, a biomarker that is measured on clinical laboratory platforms, thus providing a degree of clinical relevance, reproducibility and robustness to our findings. Both cohorts consisted of typical patients at risk of adverse outcome after cardiac surgery, thus providing information relevant to similar patients elsewhere. In both cohorts all patients were included with complete follow up for primary and secondary endpoints.

Our study carries some limitations. We studied a relatively small sample size increasing the chance of Type II error. Hypothesis-generating studies frequently use convenience-based sample size, as we did, which may carry the potential of selection bias. However, such sample selection occurred without any knowledge of biomarker results or clinical outcome and is unlikely to have been affected by a significant degree of selection or ascertainment bias. Moreover, despite baseline differences in type and duration of cardiac surgery in the exploration and validation cohorts, biomarker-informed risk assessment was superior to conventional clinical risk assessment. Finally, our study had only one risk assessor, but involvement of more risk assessors would have been logistically challenging because they were not allowed to be involved in the treatment of enrolled patients. However, we are the first to report on a kidney biomarker-informed risk prediction and demonstrated a clear signal in two independent study cohorts. Future studies should focus on interobserver agreement for conventional- and biomarker-guided risk assessment and address the question, whether assessment of patients after cardiac surgery depends on the qualification/degree of experience of the treating clinician, whether improved assessment may translate into improved adherence to KDIGO guidelines recommended AKI care bundles and whether such revised care would translate into better patient outcomes.

Conclusion

In conclusion, we found that, within a given clinical context, risk prediction for MAKE or AKI using conventional clinical risk assessment (CCA) was inferior to prediction with combined kidney injury biomarker and clinical information (B&CI). Also, we found that the improved predictive ability associated with the use of NGAL derived mostly from improvements in the identification of patients not developing adverse events. These observations support the need to conduct interventional studies comparing combined kidney B&CI risk assessment guided therapy versus CCA-guided patient management.

Summary points

Study findings

- Biomarker informed risk-assessment is superior in predicting major adverse kidney events and acute kidney injury after open-heart surgery.
- Compromised by low event rates, predominantly patients' risk not developing events was reduced.

Conclusion

- neutrophil gelatinase-associated lipocalin test result at the bedside may help guiding early risk-stratified interventions such as implementation of the 'Kidney Disease Improving Global Outcome' care bundles.
- Further research on biomarker test result-informed clinical decision-making is needed.

Financial & competing interests disclosure

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No writing assistance was utilized in the production of this manuscript.

Ethical conduct of research

The authors state that they have obtained appropriate institutional review board approval or have followed the principles outlined in the Declaration of Helsinki for all human or animal experimental investigations. In addition, for investigations involving human subjects, informed consent has been obtained from the participants involved.

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